



Density Functional Theory (B3LYP/6-311+G(d, p)) Study of Stability, Tautomerism and Acidity of 2-Thioxanthine in Gas and Aqueous Phases

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Abstract: This work is a contribution of theoretical chemistry to the knowledge of 2-thioxanthine's properties. Its aim first consists in checking the chemistry's results related to the exploitation of semi-empirical methods; it provides theoretical data on the acidity of 2-thioxanthine tautomers. To do this, the DFT method with the B3LYP functional, associated with the 6-311+G(d, p) basis set was used. The aqueous phase was modelled with the Polarizable Continuum Model (PCM). The results show that in gas and aqueous phases 2-thioxanthine can exist as a mixture of four tautomers 2TX(1,3,7), 2TX(1,3,9), 2TX(1,7,10) and 2TX(1,9,10). The relative stability decreases in the order 2TX(1,3,7) > 2TX(1,3,9) > 2TX(1,9,10) > 2TX(1,7,10). This work establishes that the tautomer 2TX(1,9,10) comes from the 2TX(1,3,7) via the 2TX(1,3,9) one. It demonstrates that the acidity of the most stable tautomer's nitrogen 2TX(1,3,7), decreases in the order 7 > 3 > 1 in gas phase and in the order 3 > 7 > 1 in aqueous phase. It provides data to elucidate the mechanisms to understand biological activities of 2-thioxanthine.

Keywords: 2-Thioxanthine, Stability, Tautomerism, Acidity, B3LYP

1. Introduction

2-Thioxanthine is a derivative of xanthine in which the oxygen atom in the 2-position is replaced by a sulfur atom. It is based on thiopurines, which are rare components of t-RNA. Some of them possess important biological and pharmacological properties [1-10]. The similarity of their structures to those of oxopurines permits their recognition by proteins and their incorporation in nucleic acids [1-3]. Sulfur-substituted nucleic acid bases have been developed as clinical drugs [11-15], where 2-thioxanthine evokes intensives intrests. Recently, 2-thioxanthine was the subject of an experimental study that allowed its determination from electrochemical sensor modified using poly-melamine and polyglutamic [16].

Most of the activities of thiopurines is expected to depend

on the tautomeric équilibre of the molécule [17, 18]. Several experimental studies are reported on the tautomerism of 2-thioxanthine in literature. Indeed 2-thioxanthine has 14 shapes and three types of equilibria can be observed: keto \rightleftharpoons enol, thione \rightleftharpoons thiol and N7(H) \rightleftharpoons N9(H). The UV spectra of 2-thioxanthine shows that the predominant tautomer exists in an oxothione form with the imidazole proton on N9-H [19]. Additionally, ¹HNMR measurements establish that the predominant tautomer exists in an oxothione form with the imidazole proton on N(7) [20]. Although this molecule has been the subject of several researches, the theoretical ones of Pervin Unal Civcir have given a renewed interest. It has been studied by the semi-empirical calculation methods AM1 and PM3, 2-thioxanthine [21], 6-thioxanthine [22], 2,6-dithioxanthine [23] and other

molecules [24,25]. The research establishes that for 2-thioxanthine, the oxothione N7(H) form is more stable than the oxothione N9(H) form in the gas phase while the oxothione N9(H) form is predominant in aqueous phase [21]. Li [26] did the same investigations with B3LYP/6-311G(d, p) method, he also show that oxothione N7(H) form is the most stable tautomer while N9(H) form is the next.

The verification of semi-empirical methods' chemistry results remains at the centre of our team's concern. Furthermore, to our knowledge, there are no theoretical data on the acidity of 2-thioxanthine. To do this, we use DFT method with the B3LYP functional. This process yields convincing results for 6-thioxanthine, dithioxanthine and xanthine [27-29]. In this impetus, the present research aims to question those deducted from semi-empirical methods relating to 2-thioxanthine. Specifically, it focused on the stability, tautomerism and acidity of its tautomers.

2. Methods of Calculation

All calculations were carried out with DFT (B3LYP functional) using 6-311+G(d, p) basis set [30], as incorporated in the GAUSSIAN-03 program [31]. In aqueous phase, the solvation model Polarizable Continuum Model (PCM) was used [32, 33]. The geometries of tautomers, transition states and intermediates have been fully optimized. The Gibbs free energies are obtained from the calculation of the frequencies. Frequency analyses were proceeded to confirm the structure being a minimum or a transition state (i.e without or with solely an imaginary frequency). To name the 14 tautomeric forms we have used the following notations: 2TX(i, j, k) where i, j, and k stand for the amount of the nitrogen, oxygen or sulfur atoms to which the hydrogen is attached (Figure 1).

Moreover, to establish the presence of a tautomerism, this work determines, first of all, the possible equilibriums. Then, it highlights those that are likely to exist. It calculates their constants and their activation energies. The following section presents the results obtained.

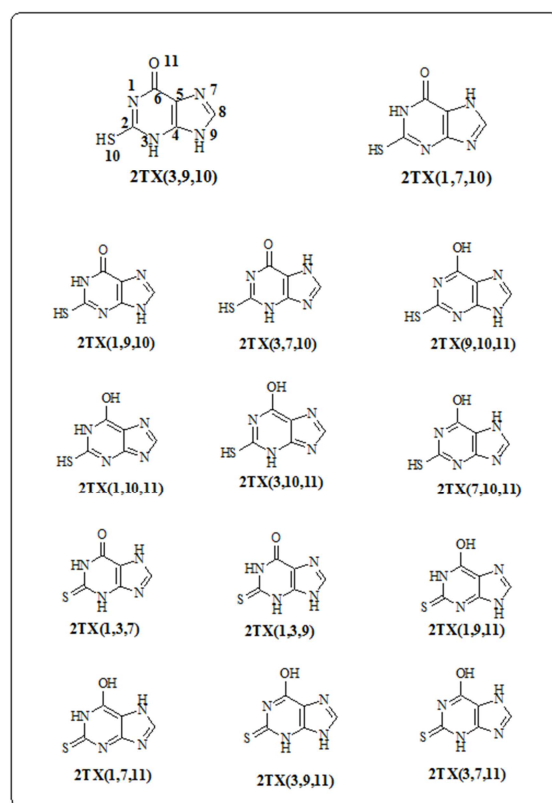


Figure 1. Tautomers of 2-Thioxanthine.

3. Results and Discussions

The results concern the stability, the tautomerism of 2-thioxanthine and the acidity of its heteroatoms.

3.1. Stability of 2-Thioxanthine's Tautomers

The Gibbs free energy, at computational level B3LYP/6-311+G(d, p), helps to discuss the relative stability of the 14 tautomers shown in Figure 1. Table 1 summarizes its values; ΔG is the difference between the Gibbs free energy of the most stable tautomer 2TX(1, 3, 7) and those of the others [34, 35].

Table 1. Gibbs Free Energy G (a. u) and ΔG (Kcal/mol) at $T = 298,15$ K.

Tautomères	Gas phase		Aqueous phase	
	Gg (au)	ΔG_g (Kcal/mol)	Gaq (au)	ΔG_{aq} (Kcal/mol)
2TX(3,9,10)	-885.450279	26.39	-885.508951	16.76
2TX(1,7,10)	-885.475589	10.51	-885.520461	9.54
2TX(1,9,10)	-885.477139	9.54	-885.520865	9.28
2TX(3,7,10)	-885.468658	14.86	-885.514217	13.46
2TX(9,10,11)	-885.472897	12.20	-885.511687	15.04
2TX(1,10,11)	-885.430981	38.50	-885.492285	27.22
2TX(3,10,11)	-885.452211	25.18	-885.497735	23.80
2TX(7,10,11)	-885.468590	14.90	-885.510371	15.87
2TX(1,3,7)	-885.492344	0.00	-885.535661	0.00
2TX(1,3,9)	-885.479001	8.37	-885.53203	2.28
2TX(1,9,11)	-885.451139	25.86	-885.513096	14.16
2TX(1,7,11)	-885.440027	32.83	-885.508762	16.88
2TX(3,9,11)	-885.458153	21.45	-885.514865	13.05
2TX(3,7,11)	-885.468658	14.86	-885.517589	11.34

ΔG_g : ΔG in the gas phase, ΔG_{aq} : ΔG in the aqueous phase

The discussion focuses on the gas phase at first. The results in Table 1 show that the oxothione tautomer 2TX(1,3,7) is the most stable of the 14 tautomers. The oxothione 2TX(1,3,9) follows it. Their energy differs from 8.37 kcal/mol. The third most stable tautomer corresponds to the oxothiol 2TX(1,9,10). Its relative energy is 9.54 kcal/mol. The fourth more stable tautomer is the oxothiol tautomer 2TX(1,7,10), which is 10.51 kcal/mol above the 2TX(1,3,7). According to Mesey and al [34,35], 10 kcal/mol is a reasonable limit for predicting the presence of stable species. This work suggests that 2-thioxanthine can exist in the gas phase under a mixture of four tautomers that are 2TX(1,3,7), 2TX(1,3,9), 2TX(1,9,10) and 2TX(1,7,10); but the tautomer 2TX(1,7,10) can exist in small amount at room temperature. The relative stability decreases in the order 2TX(1,3,7) > 2TX(1,3,9) > 2TX(1,9,10) > 2TX(1,7,10). Thus the most stables tautomers are oxothione forms.

Comparing the previous finding with those of the aqueous phase, it is observed that the Gibbs free energy difference is positive for all the tautomers except for two tautomers that are enolthiol 2TX(9,10,11) and 2TX(7,10,11). This result suggests that the presence of water helps to stabilize them with a clear stabilization of tautomers 2TX(1,3,9) and 2TX(1,7,10). The Gibbs free energy difference of tautomers 2TX(1,3,9), 2TX(1,7,10) and 2TX(1,9,10) with the most stable tautomer 2TX(1,3,7) is 2.28; 9.54 and 9.28 kcal/mol respectively. In this state, according to Mezey et al [34,35], four tautomers can exist in order of decreasing stability following 2TX(1,3,7) > 2TX(1,3,9) > 2TX(1,9,10) > 2TX(1,7,10). The existence of these tautomers had already

been predicted by Civcir [21] but with a different order of stability: 2TX(1,3,7) > 2TX(1,9,10) > 2TX(1,7,10). > 2TX(1,3,9), in the gas phase and 2TX(1,3,9) > 2TX(1,3,7) > 2TX(1,9,10) > 2TX(1,7,10), in aqueous phase. The DFT/B3LYP/6-311+G(d, p) method we used is more elaborate, so the resulting orders of stability are the most likely.

3.2. Tautomerism of 2-Thioxanthine

To evaluate the tautomerism of 2-thioxanthine, we first consider the possible equilibria between the potential tautomers and then we calculate the equilibrium constants and activation energies.

3.2.1. Probable Tautomeric Equilibria in 2-Thioxanthine

Most therapeutic activities of thiopurines depend on potential equilibria between their tautomeric forms [17, 18]. Here, it is accepted that the exchange of hydrogen atoms remains possible only between neighbouring heteroatoms or separated by at most two atoms. Moreover, this research prohibits simultaneous transfers of more than two hydrogen atoms. Under these conditions, there are four potential equilibria between the most stable tautomers of 2-thioxanthine. The Figure 2 shows that the most stable tautomer 2TX(1,3,7) can be in equilibrium with 2TX(1,7,10) or 2TX(1,3,9). The tautomer 2TX(1,7,10) can also be in equilibrium with 2TX(1,9,10), which is itself with 2TX(1,3,9). Their actual existence suggests calculating their constants and activation energies.

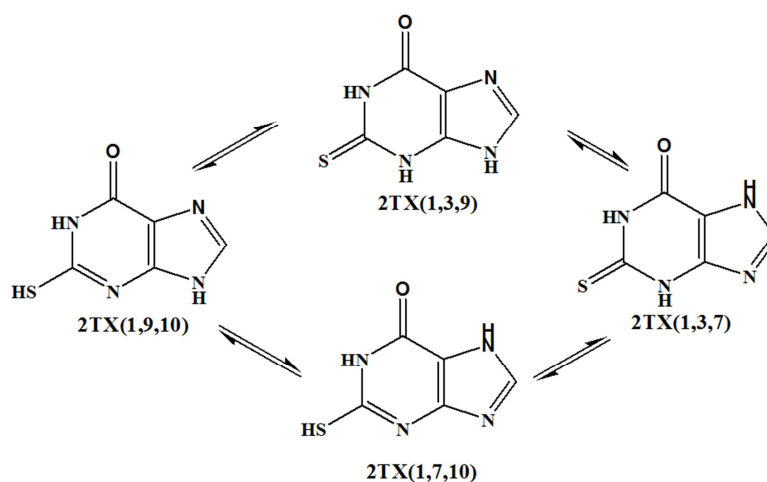


Figure 2. Possible equilibria between the most stable tautomers of 2-Thioxanthine.

3.2.2. Tautomeric Equilibrium Constants

A chemical equilibrium between two tautomers A and B ($A \rightleftharpoons B$) is characterized by its constant K_T . The calculation of K_T makes it possible to highlight the real 2-thioxanthine's tautomeric equilibrium. K_T 's values are obtained with the relation:

$$K_T = \exp\left(-\frac{\Delta G}{RT}\right) \quad (1)$$

The Table 2 collects the K_T values in gas or aqueous phase at B3LYP/6-311+G(d, p).

Table 2. Equilibrium Constants K_T at $T = 298,15$ K.

Equilibrium	K_{Tg}	K_{Taq}
$2TX(1,9,10) \rightleftharpoons 2TX(1,3,9)$	7.19	$1.37 \cdot 10^5$
$2TX(1,3,9) \rightleftharpoons 2TX(1,3,7)$	$1.37 \cdot 10^6$	$4.68 \cdot 10^1$
$2TX(1,9,10) \rightleftharpoons 2TX(1,7,10)$	$1.94 \cdot 10^{-1}$	$6.52 \cdot 10^{-1}$
$2TX(1,7,10) \rightleftharpoons 2TX(1,3,7)$	$5.10 \cdot 10^7$	$9.82 \cdot 10^6$

When $K_T < 10^{-4}$, the form A exists alone. If $K_T > 10^4$, compound B predominates. The equilibrium becomes effective if K_T ranging from 10^{-4} to 10^4 .

The K_T value of the $2\text{TX}(1,3,9) \rightleftharpoons 2\text{TX}(1,3,7)$ and $2\text{TX}(1,7,10) \rightleftharpoons 2\text{TX}(1,3,7)$ processes are respectively $1.37 \cdot 10^6$ and $5.10 \cdot 10^7$ in the gas phase; they suggest a clear stability of $2\text{TX}(1,3,7)$ in equilibrium; it can't be transformed into the forms $2\text{TX}(1,3,9)$ and $2\text{TX}(1,7,10)$. The $2\text{TX}(1,9,10) \rightleftharpoons 2\text{TX}(1,3,9)$ and $2\text{TX}(1,9,10) \rightleftharpoons 2\text{TX}(1,7,10)$ processes have respective K_T values of 7.19 and $1.94 \cdot 10^{-1}$. These values indicate that the tautomers are present in comparable quantities. The K_T value of transformations $2\text{TX}(1,9,10) \rightleftharpoons 2\text{TX}(1,3,9)$ and $2\text{TX}(1,3,9) \rightleftharpoons 2\text{TX}(1,3,7)$ passes respectively 7.19 and $1.37 \cdot 10^6$ in the gas phase at $1.37 \cdot 10^5$ and $4.68 \cdot 10^1$ in the aqueous one. This is due to the clear stabilization of tautomer $2\text{TX}(1,3,9)$ in this latter one. Nevertheless $2\text{TX}(1,3,7)$ remains the most stable.

3.2.3. Activation Energies of Possible Tautomeric Equilibriums

The Figure 3 illustrates two access pathway to the most stable tautomer $2\text{TX}(1,3,7)$ starting from $2\text{TX}(1,9,10)$. The table 3 show the Gibbs free energies of all the species involved in tautomerism as well as the imaginary frequencies of the different transition states; these last quantities characterize them. The table 4 contains activation energies. This article also explains the energy profile of 2-thioxanthine's tautomerism (Figure 4)

In the first pathway (Figure 4), The hydrogen atom bonded

to the sulfur atom S10 of the tautomer $2\text{TX}(1,9,10)$ transfers onto the nitrogen atom N3. This result carried out through the transition state TS1 with an energy barrier of 27.44 Kcal/mol to give $2\text{TX}(1,3,9)$. Then, in $2\text{TX}(1,3,9)$, the hydrogen atom bonded to the nitrogen atom N9 firstly transfers onto the carbon atom C8 via the transition state TS2, with an energy barrier of 47.63 Kcal/mol to give intermediate IM1. In the second step, the same hydrogen atom passes from this latter one onto tautomer $2\text{TX}(1,3,7)$ via the transition state TS3; this process corresponds an energy barrier of 28.43 Kcal/mol.

In the other pathway, in $2\text{TX}(1,9,10)$, the hydrogen atom bonded to the nitrogen atom N9 firstly transfers onto the carbon atom C8. This displacement is realized through the transition state TS4, with an energy barrier of 54.17 Kcal/mol to give intermediate IM2, then it passes from IM2 onto tautomer $2\text{TX}(1,7,10)$ via the transition state TS5, with a barrier energy of 25.75 Kcal/mol. Finally, the hydrogen atom bonded to the sulfur atom S10 in $2\text{TX}(1,7,10)$ transfers onto the nitrogen atom N3 via the transition state TS6, with an energy barrier of 23.15 Kcal/mol to give $2\text{TX}(1,3,7)$.

The highest activation energy in both pathways is obtained at the breaking of the bond N9-H (47.63 and 54.17 Kcal/mol respectively). That of the second is 6.54 Kcal/mol higher than that of the first. This latter remains thus the most favourable for the reaction between 2-Thioxanthine's tautomers which may exist. In other words, the tautomerism is preferentially realized by the first pathway.

The preceding results make it possible to discuss the 2-thioxanthine's heteroatom acidity.

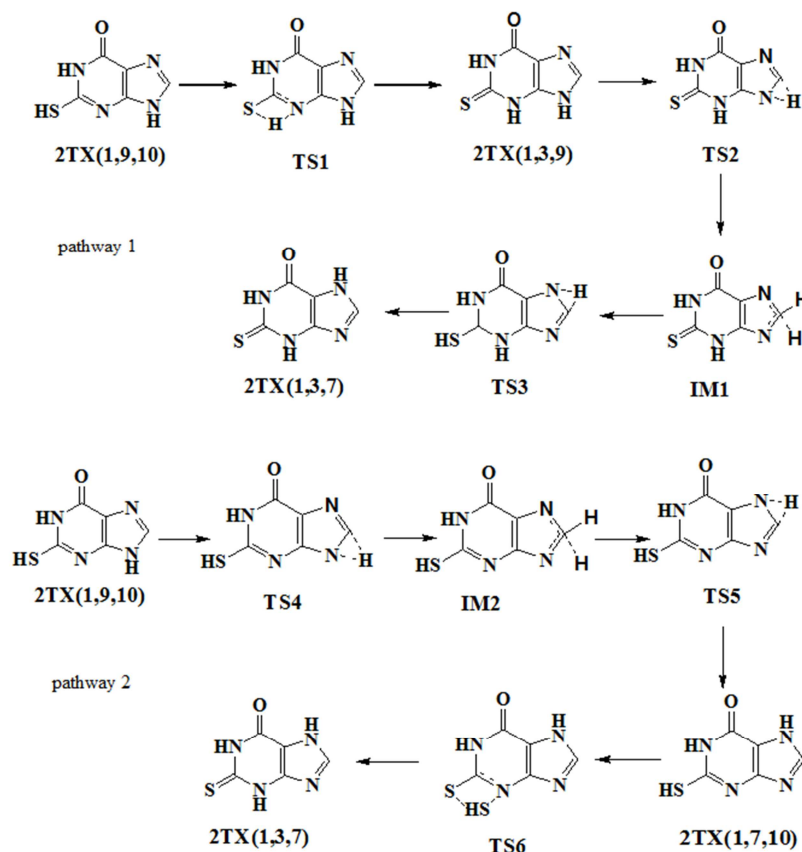


Figure 3. Potential Tautomerism of 2-Thioxanthine.

This article also explains the energy profile of 2-Thioxanthine's tautomerism (Figure 4).

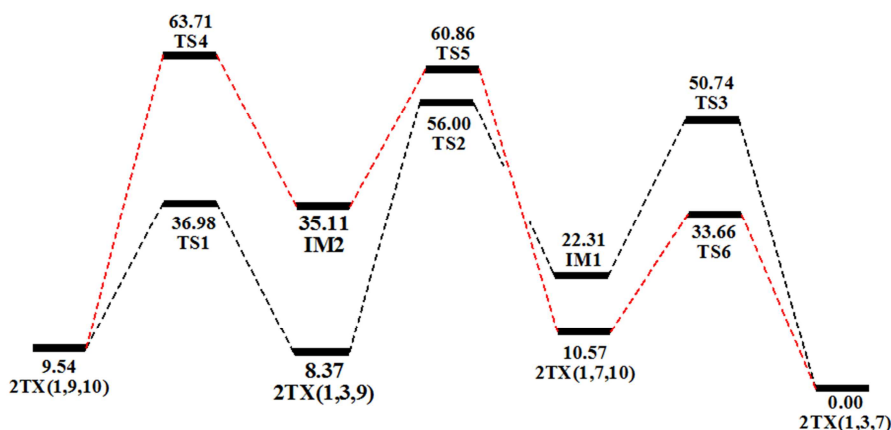


Figure 4. The relative Energy Profiles of the two pathways tautomerization of 2-thioxanthine.

Table 3. Gibbs Free Energies and Imaginary Frequencies in gas phase.

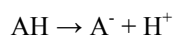
Espèces	G (au)	ΔG (kcal/mol)	Imaginary Frequencies
2TX(1,3,7)	-885.492344	0.00	
2TX(1,3,9)	-885.479001	8.37	
2TX(1,7,10)	-885.475589	10.51	
2TX(1,9,10)	-885.477139	9.54	
IM1	-885.456783	22.31	
IM2	-885.436393	35.11	
TS1	-885.433405	36.98	-1654.94
TS2	-885.403097	56.00	-1569.27
TS3	-885.411476	50.74	-1498.04
TS4	-885.390822	63.71	-1517.03
TS5	-885.395353	60.86	-1474.53
TS6	-885.438701	33.66	-1651.11

Table 4. Activation Energies E_a (kcal/mol) in gas phase at $T = 298, 15\text{ K}$.

TS	Reactions	E_a (kcal/mol)
TS1	2TX(1,9,10) → 2TX(1,3,9)	27.44
TS2	2TX(1,3,9) → IM1	47.63
TS3	IM1 → 2TX(1,3,7)	28.43
TS4	2TX(1,9,10) → IM2	54.17
TS5	IM2 → 2TX(1,7,10)	25.75
TS6	2TX(1,7,10) → 2TX(1,3,7)	23.15

3.3. Acidity of the Potential Tautomers

The tautomers of 2-thioxanthine have hydrogenated sites that may be deprotonated. The choice of these depends on the acid's strength [36]. The relative Gibbs free energy (ΔG) of the associated general reaction ($AH \rightarrow A^- + H^+$) helps evaluate the 2-thioxanthine's heteroatom acidity.



$$\Delta G = G(A^-) + G(H^+) - G(AH) \quad (2)$$

In gas phase, $G_g(H^+) = 2.5 RT - T\Delta S = 1.48 - 7.76 G_g(H^+) = -6.28 \text{ kcal/mol}$ [37]

In aqueous phase, $G_{aq}(H^+)$ is calculated from the relation:

$$G_{aq}(H^+) = G_g(H^+) + G_{solv}(H^+)$$

G_{solv} is the Gibbs free energy of solvation, $G_{solv}(H^+) = -263.47 \text{ kcal/mol}$ [38].

Table 5 presents the results of the calculations.

The acidity of tautomeric sites is related to the value of ΔG [36]. The weaker this is, the more the heteroatom of the position concerned is acidic. Under these conditions, in the gas phase, the nitrogen N7 of the imidazole ring is the most acid site of the tautomer 2TX(1,3,7). The nitrogen N9 is the most acid one of 2TX(1,3,9) and sulfur S10 that of 2TX(1,7,10) and 2TX(1,9,10). In the aqueous one the nitrogen N3 of the pyrimidine ring becomes the most acid site of 2TX(1,3,7) and 2TX(1,3,9). At the same time, sulfur S10 remains the most acid site of 2TX(1,7,10) and 2TX(1,9,10)

In the end, the acidity of the most stable tautomer 2TX(1,3,7) decreases in the order $7 > 3 > 1 > 8$, in gas phase and in the order $3 > 7 > 1 > 8$ in aqueous phase.

Table 5. ΔG (Kj/mol) of Potential Tautomers.

Tautomers	ΔG_g	ΔG_{aq}
2TX(1,3,7)		
N ₁	329.01	19.43
N ₃	322.09	15.47
N ₇	314.15	16.92
C ₈	350.56	47.85
2TX(1,3,9)		
N ₁	330.08	20.04
N ₃	310.78	12.17
N ₉	305.75	14.66
C ₈	354.65	49.74
2TX(1,7,10)		
N ₁	321.76	18.22
N ₇	323.53	19.77
S ₁₀	311.59	5.96
C ₈	361.47	50.70
2TX(1,9,10)		
N ₁	325.68	18.87
N ₉	323.02	20.03
S ₁₀	309.60	5.15
C ₈	364.87	52.32

4. Conclusion

The study concerns the stability, tautomerism and acidity of 2-thioxanthine from literature results. In particular, it relies

on elaborate methods of theoretical chemistry to take stock of its tautomeric forms and the acidity of its heteroatoms.

Its results establish that 2-thioxanthine can exist in gas and aqueous phases as a mixture of four tautomers 2TX(1,3,7), 2TXX(1,3,9), 2TX(1,7,10) and 2TXX(1,9,10). In the gas phase the tautomer 2TX(1,7,10) can exist in small amount at room temperature. The tautomer 2TX(1,3,7), is the most stable in both phases.

The equilibrium constant reveals that in the gas phase, only the tautomeric equilibrium $2TX(1,9,10) \rightleftharpoons 2TX(1,3,9)$ and $2TX(1,9,10) \rightleftharpoons 2TX(1,7,10)$ are possible. In the presence of water, the equilibrium $2TX(1,3,9) \rightleftharpoons 2TX(1,3,7)$ is superimposed on that of $2TX(1,9,10) \rightleftharpoons 2TX(1,7,10)$. This work suggests that the biological activity of 2-thioxanthine relies on these two mainly tautomeric equilibrium.

Activation energies in the gas phase show that the 2-thioxanthine's tautomerization is realized by the transformation of tautomer 2TX(1,9,10) to 2TX(1,3,7) through 2TX(1,3,9).

In terms of acidity, research establishes that in the gas phase, N7 represents the most acidic atom of tautomer 2TX(1,3,7). The nitrogen N9 corresponds to that of 2TX(1,3,9) whereas the sulfur S10 that of 2TX(1,7,10) and 2TX(1,9,10). In aqueous phase, this work shows that the results are preserved except those of 2TX(1,3,7) and 2TX(1,3,9); for these tautomers, N3 becomes the most acidic. In addition, this study indicates that the acidity of the most stable tautomer 2TX(1,3,7) decreases in the order $7 > 3 > 1 > 8$, in gas phase and in the order $3 > 7 > 1 > 8$ in aqueous phase. Moreover, this work opens up new perspectives; in particular, its results could help to identify the mechanisms underlying specific biological properties of 2-thioxanthine.

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